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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,304	12/28/2001	Jonathan A. Ellman	045413/0110	3985

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FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/029,304	ELLMAN ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-37 and 53-59* is/are pending in the application.

4a) Of the above claim(s) *35-37,55-57 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,53,54 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed April 20, 2004 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 34-37 and 53-59 were pending. Applicants amended claims 34 and 53. No claims were added or canceled. Therefore, claims 34-37 and 53-59 are still pending.

4. Claims 35-37, 55-57 and 59 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.

5. Therefore, claims 34, 53, 54 and 58 are examined on the merits in this action.

Withdrawn Objections/Rejections

6. All outstanding rejections and/or objections are withdrawn in view of Applicants' arguments and/or amendments.

New Rejections

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 34 is rejected under 35 U.S.C. 102(e) as being anticipated by Wells et al. (US Patent No. 6,335,155) (Filing Date is **June 26, 1998**).

For ***claim 34***, Wells et al. (see entire document) disclose libraries that are used in methods for rapidly identifying organic molecule ligands for binding to biological target molecules (see Wells et al., abstract), which anticipates claim 34. For example, Wells et al. disclose a library of candidate target binding fragments wherein said fragments are small organic molecules (e.g., see abstract, see also claim 1, "combining said biological target molecule with one or more members of a library of small, non-oligomeric soluble, synthetic organic ligand candidates"). Wells et al. also disclose library members with a disulfide-linking group (e.g., see claim 1; see also column 3, "Other embodiments of the above described methods employ libraries of organic compounds which comprise ... disulfides"; see also column 3, last paragraph; see also column 8, paragraph 3; see also column 10, line 46; see also column 16, first full paragraph). Finally, Wells et al. disclose mixing a least two candidate target binding molecules together (e.g., see column 11, paragraph 1, "Libraries of organic compounds which find use herein will

generally comprise at least 2 organic compounds, often at least about 25 different organic compounds ... preferably at least about 5000 or more different organic compounds"; see also claim 1 step (b), "combining [i.e., mixing] said biological target molecule with one or more members of a library").

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 34, 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirkpatrick et al. (U.S. Patent 6,552,060) (Filing Date is **August 11, 1998**) and

Konings et al. (Konings, D. A. M.; Wyatt, J. R.; Ecker, D. J.; Freier, S. M. "Deconvolution of Combinatorial Libraries for Drug Discovery: Theoretical Comparison of Pooling Strategies" *J. Med. Chem.* **1996**, *39*, 2710-2719).

For ***claims 34, 53 and 54***, Kirkpatrick et al. (see entire document) disclose a library of at least two disulfides with the formula CTBF-S-S-R^8 wherein R^8 is a straight chain alkyl or branched aminoalkyl or hydroxyalkyl (e.g., see figure 5; see also figures 9-11, especially figure 10 wherein R'=A, B, C, D, M and O; see also paragraph bridging columns 4-5; Table 3, especially compounds F-27, M-13 and M-29; see also column 22; see especially claims 8 and 19 wherein R^8 represents branched alkyls substituted with amino or hydroxy groups; see also column 4, last paragraph wherein n-butyl imidazolyl disulfide is disclosed; see also column 5, line 5 wherein a straight chain hydroxyalkyl is disclosed) and the CTBF (i.e., the candidate target binding fragment) binds to, for example, thioredoxin reductase/thioredoxin targets (e.g., see figure 5; see also columns 7-11).

The prior art teachings of Kirkpatrick et al differ from the claimed invention as follows:

For ***claims 34, 53 and 54***, Kirkpatrick et al. do not teach a "mixture" of library members. Kirkpatrick et al. teach contacting the library members "separately" using a microtiter plate (i.e., "one compound per one well") for screening purposes (e.g., see Kirkpatrick et al., column 22, paragraph 1, "Using a 96 well plate [i.e., a microtiter plate] format, parallel combinatorial chemistry ...

was used to synthesize a large number of unsymmetrical disulfides"; see also column 23, paragraph 1, "A second plate [i.e., microtiter plate] was used for the assessment of biological activity or as a biological screen [i.e., parallel screening using a microtiter plate]").

However, Konings et al. teach the following limitations that are deficient in Kirkpatrick et al.:

For ***claims 34, 53 and 54***, Konings et al. (see entire documents) teach the use of a "mixture" of library members wherein the reaction and/or screening is carried out in one reaction vessel instead of using separate vessels and/or separate wells of a microtiter plate. For example, Konings et al. state, "[s]ynthesis and testing of mixtures of compounds [referred to herein as mixing technology] in a combinatorial library allow much greater throughput than synthesis and testing of individual compounds [e.g., individual synthesis and/or screening using microtiter plates]" (e.g., see Konings et al. abstract) and also state that this mixing technology is generally applicable to a "variety of chemistries" (e.g., see Konings et al. page 2710, column 1, paragraph 2; see also figure 2 wherein the screening of a library of 27 compounds is shown), which would include the disulfide libraries of Kirkpatrick et al.

Therefore, it would have been *prima facie* obvious to one of ordinary skill to create and/or screen a library as disclosed by Kirkpatrick et al. using the "mixing" technology as taught by Konings et al. because the method of forming and/or screening a library (e.g., microtiter plates versus "mixing" technology) represents a mere design choice (i.e., both methods were well known in the art at

the time of filing and could be used interchangeably to produce and/or screen libraries of organic compounds). A person of ordinary skill in the art would have been motivated to use the "mixing technology" as exemplified by Konings et al. to create and/or screen a larger number of compounds in a shorter period of time than could be achieved using the "one compound, one well" approach employed by Kirkpatrick et al. (e.g., see Konings et al., page 2710, column 1, paragraph 1, "Synthesis and testing of mixtures of compounds in a combinatorial library offer the potential of much greater throughput than the 'one compound, one well' approach" i.e., use of microtiter plate; see also abstract). Furthermore, a person of ordinary skill in the art would have had a reasonable expectation of success because Konings et al. state that the method is generally applicable to all compounds (e.g., see Konings et al., page 2710, column 1, paragraph 2), which would include the disulfide structures disclosed by Kirkpatrick et al.

10. Claims 34, 53, 54 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirkpatrick et al. (U.S. Patent 6,552,060) (Filing Date is **August 11, 1998**) and Konings et al. (Konings, D. A. M.; Wyatt, J. R.; Ecker, D. J.; Freier, S. M. "Deconvolution of Combinatorial Libraries for Drug Discovery: Theoretical Comparison of Pooling Strategies" *J. Med. Chem.* **1996**, *39*, 2710-2719) and Fischli et al. (US Patent No. 4,766,133) (Date of Patent is **August 23, 1988**).

For ***claims 34, 53 and 54,*** the combined references of Kirkpatrick et al. and Konings et al. teach all the limitations stated in the 35 U.S.C. 103(a) rejection

above (incorporated in its entirety herein by reference), which renders obvious claims 34, 53 and 54.

The combined prior art teachings of Kirkpatrick et al. and Konings et al. differ from the claimed invention as follows:

For ***claim 58***, the combined prior art teachings of Kirkpatrick et al. and Konings et al. differ from the claimed invention by not specifically reciting R^8 = straight chain alkyl with 1-10 carbon atoms substituted with an amine.

However, Fischli et al. teach the following limitations that are deficient in the combined teachings of Kirkpatrick et al. and Konings et al.:

For ***claim 58***, Fischli et al. (see entire document) teach disulfide compounds with R^8 = straight chain alkyl with 1-10 carbon atoms substituted with an amine (e.g., see Fischli et al., column 13, compound G).

It would have been obvious to one skilled in the art at the time the invention was made to use the combinatorial high throughput screening techniques as taught by Kirkpatrick et al. and Konings et al. against thioredoxin reductase/thioredoxin targets (e.g., see Kirkpatrick et al., column 22, paragraph 1; see also column 23, paragraph 1) with the disulfides as taught by Fischli et al. (e.g., see Fischli et al., column 12, compound G) because Kirkpatrick et al. and Konings et al. teach that disulfides with benzimidazole and/or imidazole rings are a preferred embodiment for high throughput screening against thioredoxin reductase/thioredoxin targets (e.g., Kirkpatrick et al., abstract, see especially column 18, lines 24-25), which would encompass the compounds disclosed by Fischli et al. Furthermore, one of ordinary skill in the art would have been

motivated to use the compounds disclosed by Fischli et al. because Fischli et al. teach that their disulfides are "gastric acid secretion-inhibiting and/or mucosa-protecting" (e.g., see column 1, lines 66-67), which would be beneficial because Kirkpatrick et al. and Konings et al. teach the therapeutic application of disulfides to the stomach and/or gastrointestinal tract which would require such protection (see Kirkpatrick et al., "The term 'cancer' refers to ... stomach cancer"; see also column 3, line 39; see also column 8, line 58). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because all three references teach the application of similar compounds (e.g., all three references teach asymmetric disulfides with heteroaromatic rings).

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
June 27, 2004